Semi-annual Status Report
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Stanford University, November 1, 1966

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Title: Analysis of Human Korotkov Sounds

Progress to date is summarized in the four areas of research presented in the corresponding numbered paragraphs below, including: (1) the development of an automatic incremental blood pressure cuff deflation system; (2) spectral analysis of Korotkov sounds; (3) determination of stethoscope effectiveness in transducing Korotkov sounds; (4) R-K pulse-wave arrival time.

In general, the initial period of the grant has been devoted to data collection, preliminary analysis, and development of analytical methods and supporting digital systems. During the next period, full-scale analysis of collected data will begin.

(1) Automatic incremental blood pressure cuff deflation system

A special system for control of cuff air pressure was found necessary for the quantitative analysis of Korotkov sounds. This system has been designed and built, and has proven useful not only in recording data for this research, but also in routine patient monitoring. It may be useful in monitoring astronauts. Rationale for the development of the system and sample chart recordings are found in Appendix I. Appendix II contains circuit description, physical description and block diagrams.

(2) Spectral analysis of Korotkov sounds

A large quantity of data suitable for spectral analysis has been recorded on magnetic tape. The principle sources of these data include approximately 25 normal subjects who received general anesthesia or vasopressor drugs under carefully controlled laboratory conditions, as well as a group of surgical patients in the operating room. We are searching for spectral changes that can be related to the stress of vasopressor drugs, general anesthesia, and surgical operations. The anticipated changes are being correlated with the cardiac output, peripheral resistance, direct arterial blood pressure, pulse volume, acid-base balance, R-K arrival time (see section below) and other physiologic measurements.

Spectral analysis with analog methods proved unsatisfactory in this project. Therefore, we have turned to proven digital methods, developed and extensively used by the Stanford Electronics Laboratories in data analysis performed under Department of Defense contracts.

At the time the grant request was submitted to NASA (June 1966) the plan was to perform spectral analysis on the IBM 7094 digital computer located

at the Ames Research Center. This approach seemed reasonable as the computer at Ames was available and we had successfully performed spectral analysis of Korotkov sounds a year earlier on our IBM 1620 and IBM 7090 computers. The major problem would have been analog-to-digital conversion (probably at a commercial computer facility) of our data. However, alternative computer facilities became available at Stanford (at no cost to NASA) and it was decided that data analysis would be more logically undertaken on our new interdepartmentally-controlled Digital Equipment Corporation PDP-8 digital computer and the new institutional IBM 360-50 facility located at the Stanford Medical Center. The major obstacle has been the design and performance evaluation of the data link and interfacing between the PDP-8 computer and the IBM 360-50. Although the link has worked, we remain dissatisfied with results. We are currently striving to improve its operation. Meanwhile, the IBM 7090 computer program for the digital spectrum analyzer has been modified and checked out on the IBM 360-50. Spectral analysis of Korotkov sounds on a "production" basis will commence as soon as the data link situation is resolved. If necessary, an existing PDP-8 program for spectral analysis will be revised to permit Korotkov sound processing.

(3) Stethoscope effectiveness in transducing Korotkov sounds

The capability of stethoscopes to transduce Korotkov blood pressure sounds varies greatly. This variation may have significant influence on indirect blood pressure measurements. Five different types of stethoscopes were tested in a series of 30 normal human subjects. Figure 1 indicates methods of recording and preliminary analog analysis of the stethoscope data, and Figure 2 shows the comparative responses of two types of stethoscopes. Note that the output from Stethoscope A reaches a maximum of less than 3 energy units during cuff deflation, in contrast to Stethoscope B, which early in deflation reaches an output of 29 energy units.

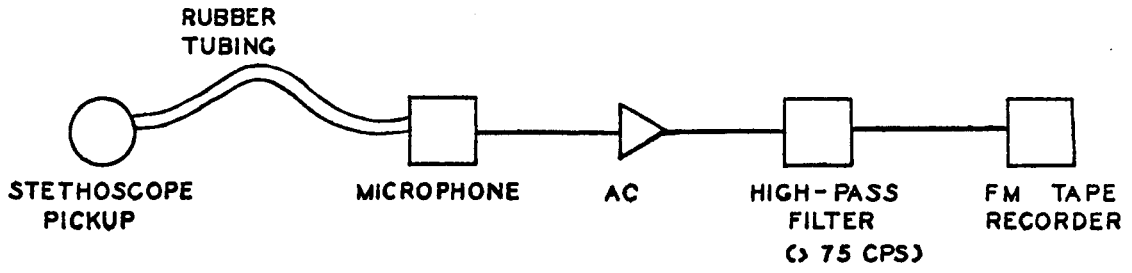
Existing analog recordings will be fully analyzed by digital methods as computer programs and computer systems become available. The results of these studies (based on initial results) have been accepted for presentation in October 1967, Annual Meeting of the American Society of Anesthesiologists, and for publication in abstract form in ANESTHESIOLOGY, January 1968.

(4) R-K pulse-wave arrival time (modified from Robard, S.: Circulation 8:600-604, 1953)

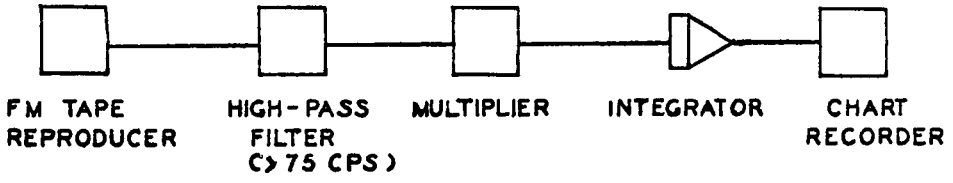
The R-K time is the interval between the peak of the R-wave and the arrival of the resulting pulse at the brachial artery. Measurements are made during deflation of the standard blood pressure cuff. According to the original description, R-K time is longer with cardiovascular depression and shorter with cardiovascular stimulation. Furthermore, the slope of

the up-stroke of the brachial pulse is measured without recourse to needles or catheters. This slope decreases with depression and increases with stimulation. Our initial results show that halothane anesthesia at moderately deep levels (MAC 2) markedly decreases the slope and increases R-K time. Figure 3 shows that control R-K time in this subject is 300 msec at systolic pressure, and 220 msec at diastolic pressure. Under anesthesia, the values increased to 450 msec at systolic and 350 msec at diastolic, and the slope is noticeably flattened.

All of our data recorded in the laboratory and the operating room are suitable for R-K analysis. Present analytical methods include direct measurement of R-K time from high-speed (100 mm/sec) chart recordings of ECG and Korotkov sounds, and a specially designed analog device. Measurements and analysis by digital computer are readily feasible, using slight modifications of programs already written in our laboratories.



RECORDING OF STETHOSCOPE OUTPUT



ANALYSIS OF STETHOSCOPE DATA

FIG 1 RECORDING AND ANALYSIS OF STETHOSCOPE DATA

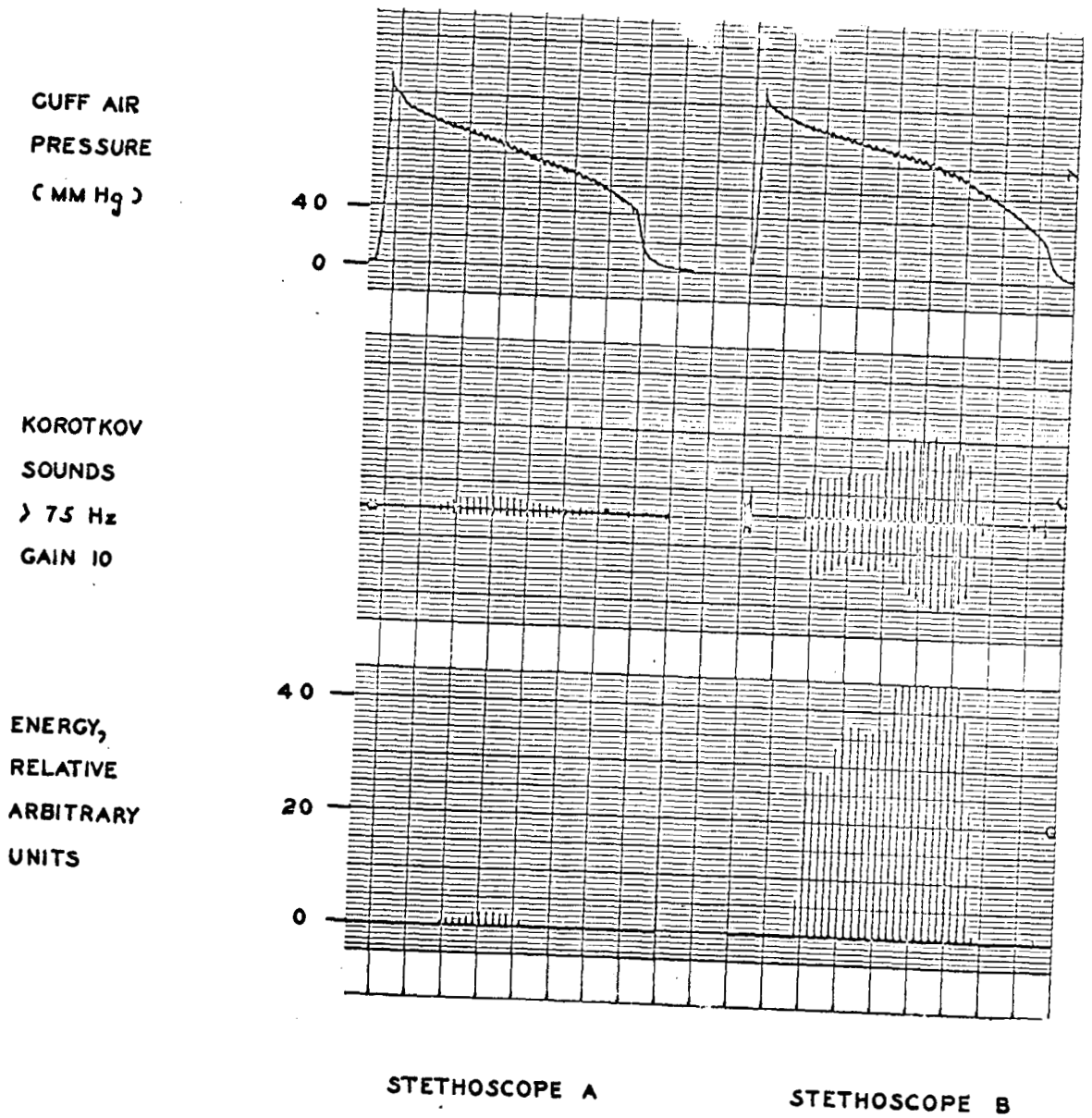


FIG 2 COMPARATIVE RESPONSES OF TWO STETHOSCOPE PICKUPS, A AND B, TO HUMAN KOROTKOV SOUNDS

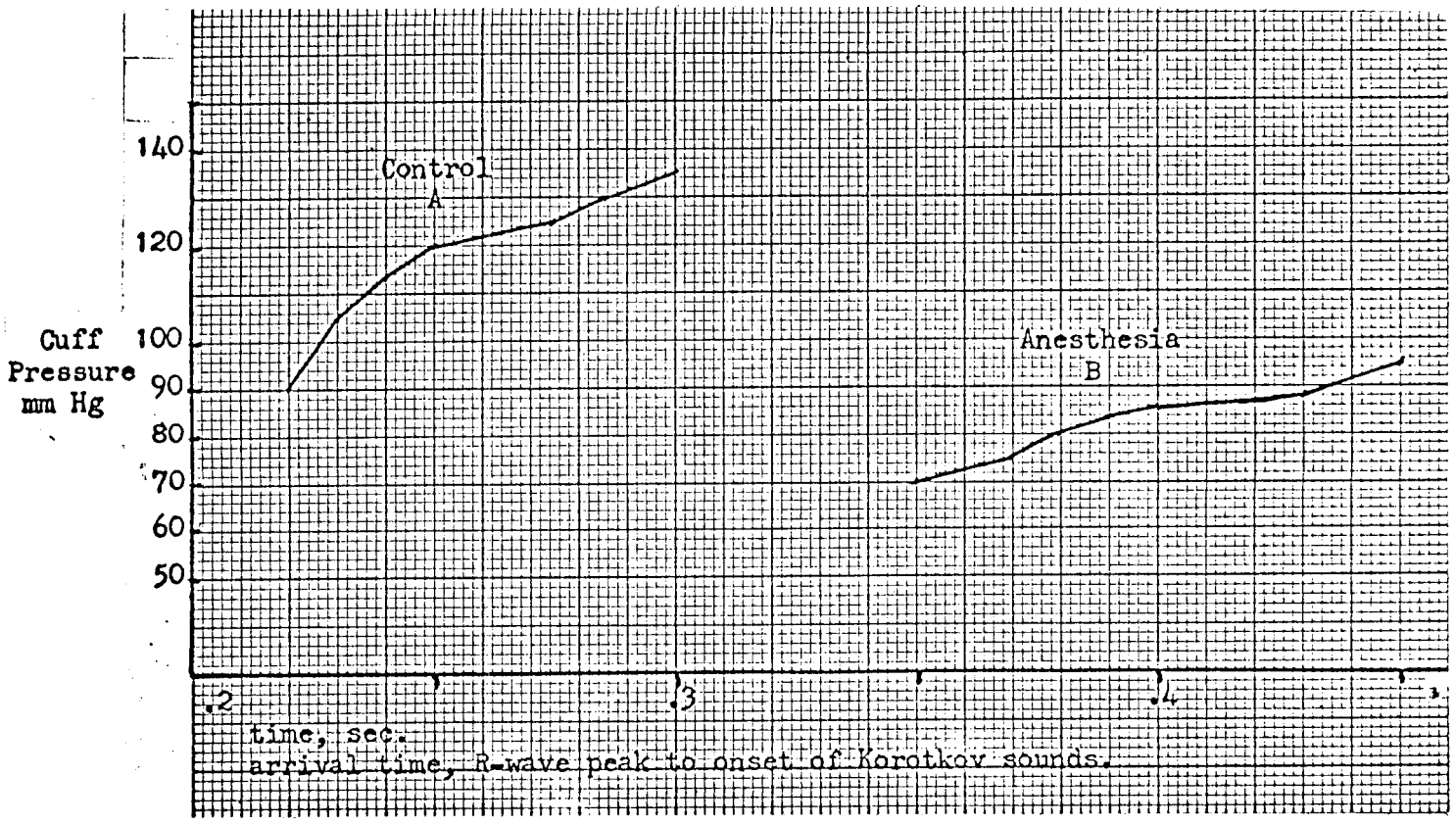


FIG 3 R - K ARRIVAL TIME

APPENDIX I. NASA Status Report, July 1967

RATIONALE ON DEVELOPMENT OF AUTOMATIC CUFF DEFLATION SYSTEM

Comment on indirect blood pressure measurement

The American Heart Association recommends rapid inflation of the blood pressure cuff to a point well above systolic pressure, then release of air pressure at the rate of 2-3 mm Hg per heart beat until systolic and diastolic determinations are completed. These determinations are made by listening for the Korotkov blood pressure sounds which are heard with the stethoscope which is positioned over the brachial artery immediately below the cuff. Systolic value is obtained by noting the cuff air pressure which coincides with the onset of the Korotkov sounds; diastolic pressure, by noting the air pressure correlating with disappearance of the sounds.

This standard method, satisfactory for the intended routine clinical purposes, is inadequate in our research on blood pressure measurement. The reasons for inadequacy of the standard methods are related to the energy distribution of Korotkov sounds as well as problems related to cuff deflation. For example, auscultation of Korotkov sounds is highly subjective and dependent on mechanical as well as physiologic variables. The correctness of the fit of the stethoscope earpieces and the level of ambient room noise affect the observed blood pressure. Moreover, in disturbed physiological states such as shock and hypothermia, the Korotkov sounds are often inaudible despite near-normal levels of intra-arterial blood pressure.

In addition to the problems of subjectiveness in auscultation, we believe there are serious limitations in the frequency response of the ear in hearing Korotkov sounds. We have data suggesting that Korotkov waveforms may, under some adverse conditions, occur entirely at subaudible frequencies. These problems are resolved through the recording of Korotkov sounds with microphone and FM tape recording systems covering appropriate bandwidth, with objective data analysis.

Comment on blood pressure cuff deflation

One objective in our work with Korotkov sounds is to develop a diagnostic test for early peripheral vasoconstriction. Such a test would require comparison of a series of Korotkov sounds recorded under control conditions with a series recorded after peripheral vasoconstriction. Furthermore, we want to compare one Korotkov sound with another in the same deflation curve, in an effort to recognize diastolic pressure objectively. Comparison should be valid only if the cuff deflation curves are comparable, a practical impossibility with the conventional hand-release deflation method. In fact, preliminary comparison of Korotkov sound spectra before and after vasoconstriction with methoxamine, using conventional cuff deflation, failed to reveal characteristic changes. It was felt that the comparison should be repeated, using data recorded with reproducible deflation curves.

Cuff deflation with the conventional hand-release valve presents several problems in addition to those cited above. For example, given the same heart rate and blood pressure, the Korotkov sounds recorded at different cuff deflation rates will differ. Figure A-I-1 shows the first 3 Korotkov sounds (stippled vertical bars) recorded at two cuff deflation rates, 3 mm Hg per heart beat in the left-hand panel A, and 0.5 mm Hg in the right-hand panel B. In both panels, heart rate is 60 per minute and systolic blood pressure is 118 mm Hg. It is obvious that the sounds in panel A are not comparable with the sounds in panel B. In fact, the third sound in panel A is approximately 5 times greater than the third sound in panel B. Clearly, cuff deflation slopes should be similar if Korotkov sounds recorded on different deflation curves are to be compared.

Critical analysis may be further confounded by the fact that the first sound is not likely to occur exactly at threshold value. Referring again to Figure A-I-1, the first sounds in both panels are unrealistically shown to occur exactly at threshold. Unfortunately, the first sound in either panel would have a much greater chance of falling haphazardly anywhere on the curve between the first and second sounds. Thus the first Korotkov sounds on different deflation curves are practically always incomparable. This error can be reduced by recording systolic pressure at very slow deflation rates.

Moreover, the Korotkov sounds are recorded under changing conditions, during deflation of the cuff, again possibly confusing critical investigation. It can be noted in Figure A-I-1 that the Korotkov sounds have appreciable duration (approximately 0.5 seconds). If they were to occur under stable conditions, the sounds would be more alike.

Cuff deflation accurately performed by the recommended method is ideally linear, the slope varying with the heart rate. Given the same pulse pressure (systolic minus diastolic blood pressure) at two different heart rates, the slopes of the deflation curves would differ, but the total number of Korotkov sounds would be identical. This is illustrated in Figure A-I-2, which compares two deflation curves, A and B, with Korotkov sounds. The essential difference between A and B is the heart rate, 120 for A and 60 for B. Note that in both cases the cuff deflation rate is 3 mm Hg per heart beat, the total number of Korotkov sounds is 14, and the pulse pressure is 40 mm Hg (120 minus 80). Inspection of these curves suggests that valid comparison might be made between the second (or third, etc.) sounds on either curve, and that the differences between the second and the 14th sounds, for example, would be comparable on either curve.

In contrast, the total number of Korotkov sounds differs if comparison is attempted between two cuff deflation curves at different pulse pressures, as illustrated in Figure A-I-3. Part A shows 8 Korotkov sounds, at a pulse pressure of 20 mm Hg (90 minus 70); part B shows 14 Korotkov sounds at the higher pulse pressure (40 mm Hg). Cuff deflation rate for A and B

is the same (3 mm Hg per heart beat), and heart rate in both curves is 120 per minute. In this case comparisons between the second and the 14th sounds between deflation curves would be impossible.

In an attempt to minimize variability in spectral analysis due to cuff deflation problems, we designed and built an automatic incremental deflation system which is fully described in Appendix II.. In brief, cuff air pressure drops in steps of adjustible height and duration, each step triggered by the R-wave of the electrocardiogram. Fully automatic blood pressure recording is achieved by combining this deflation system with a commercially available automatic cuff inflation pump.

Instrumentation for sample recordings of Korotkov sounds, made with our deflation system, is shown in Figure A-I-4, and a typical recording is seen in Figure A-I-5, in which the deflator (Channel 4) is set for 2 mm Hg per heart beat at one beat per step. Korotkov sounds within the audible range (100 Hz) are indicated on Channel 3, and it is notable that each waveform occurs on the flat portion of each deflation step. For spectral analysis the outputs from all four data amplifiers are written on analog or digital tape.

Figure A-I-6 shows a typical chart record of data which, if stored on magnetic tape, would be suitable for intensive study of early Korotkov sounds. The deflator is set to drop the cuff pressure at 2 mm Hg per heart beat, and 3 Korotkov sounds are allowed to fall on each deflation step. Note the beat-to-beat variations in audible Korotkov sounds (Channel 3), probably related to changes in cardiac output due to respirations.

Figure A-I-7 shows a chart recording of data intended for intensive study of late Korotkov sounds. The cuff (Channel 4) was first rapidly deflated (5 mm Hg per beat, one beat per deflation step) until diastolic pressure was approached, in order to minimize venous congestion. Then the deflation rate was slowed to 1 mm Hg, 3 beats per step, for a period of 14 seconds. Since these steps were too small to show well on this chart record, the steps were increased to 2 mm Hg each.

These last three figures suggest some of the possibilities for the precision control of cuff deflation for quantitative analysis of Korotkov sounds.

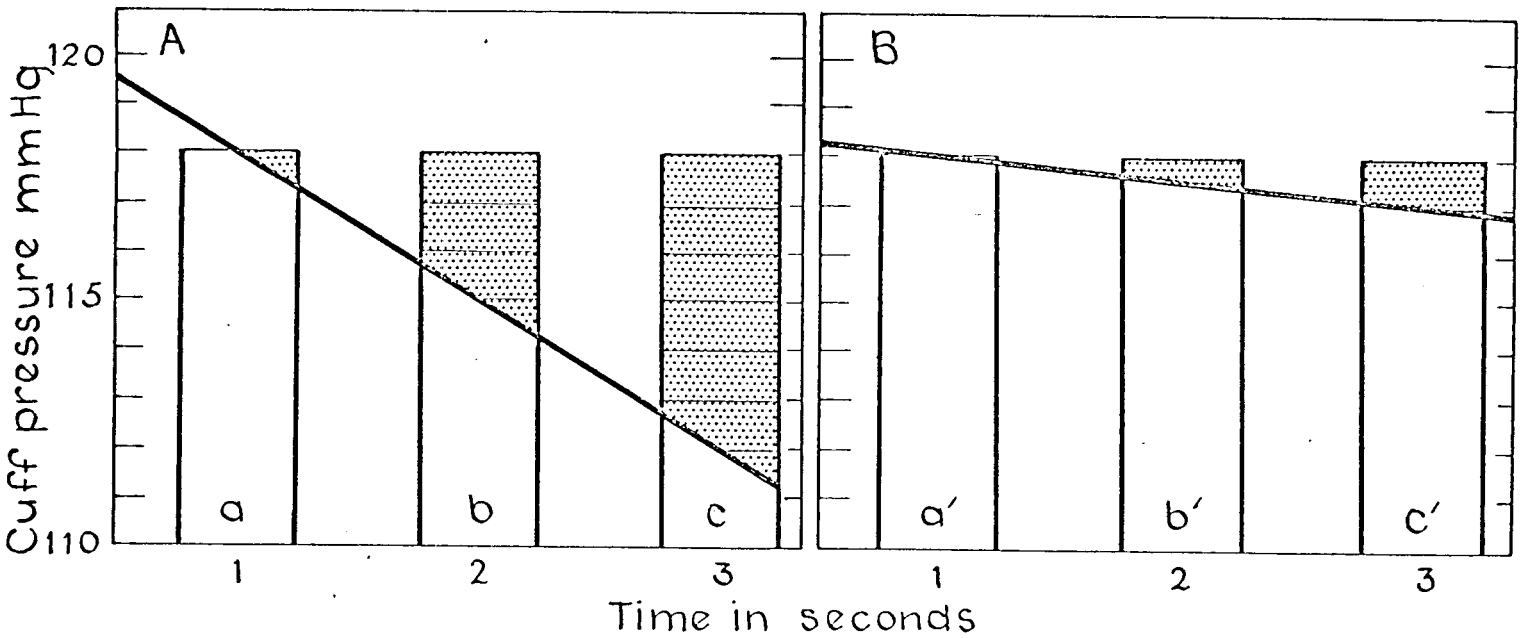


Fig. A - I - 1 Incomparability of Korotkov sounds at different cuff deflation rates.

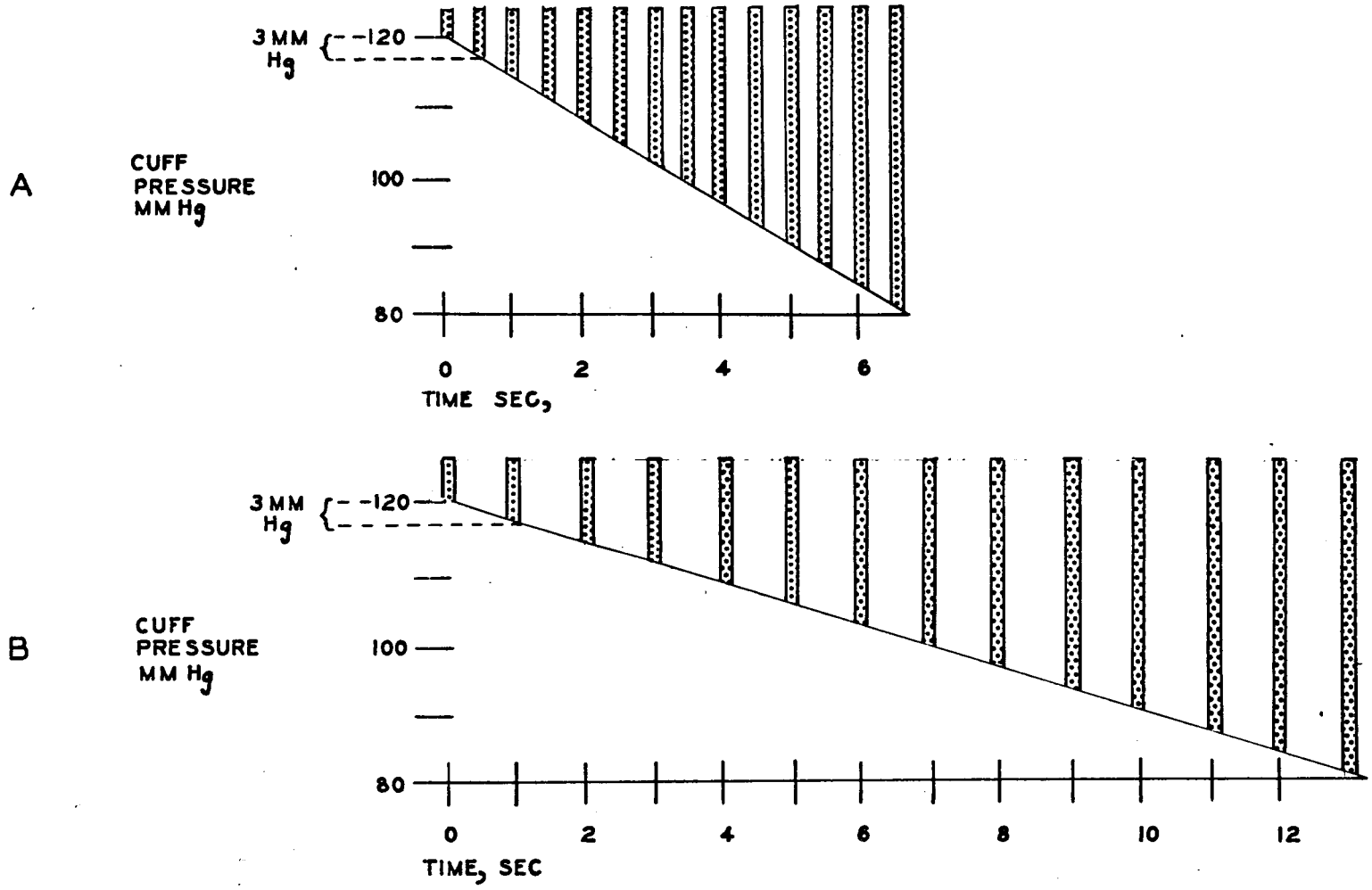


FIG A-I-2

COMPARISON OF DEFLATION CURVES AND KOROTKOV SOUNDS AT DIFFERENT HEART RATES - A-120/MIN, B-/60 MIN

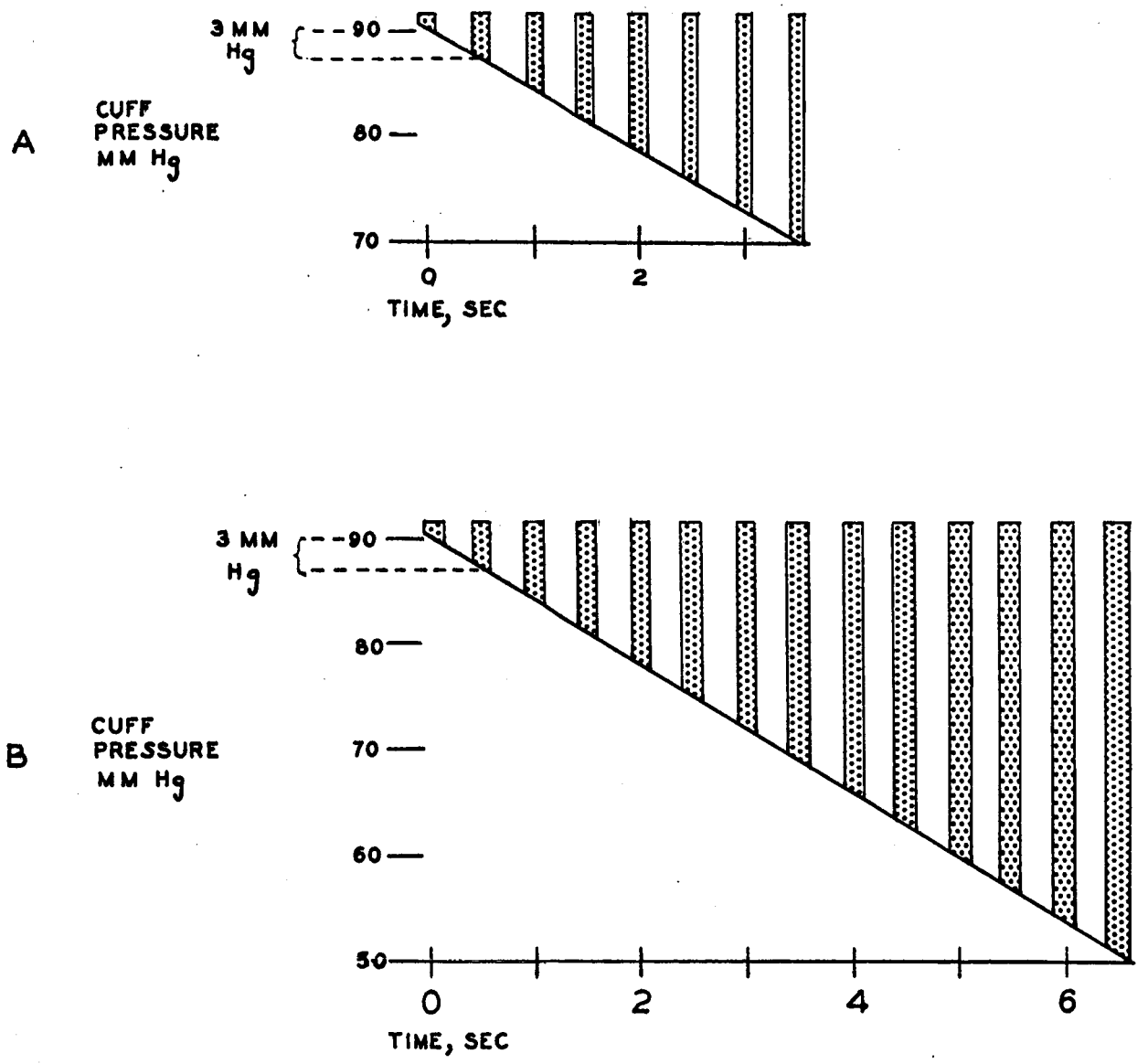


FIG A-I-3

COMPARISON OF DEFLATION CURVES AND KOROTKOV SOUNDS AT DIFFERENT PULSE PRESSURES, A-20 MM Hg, B-40 MM Hg

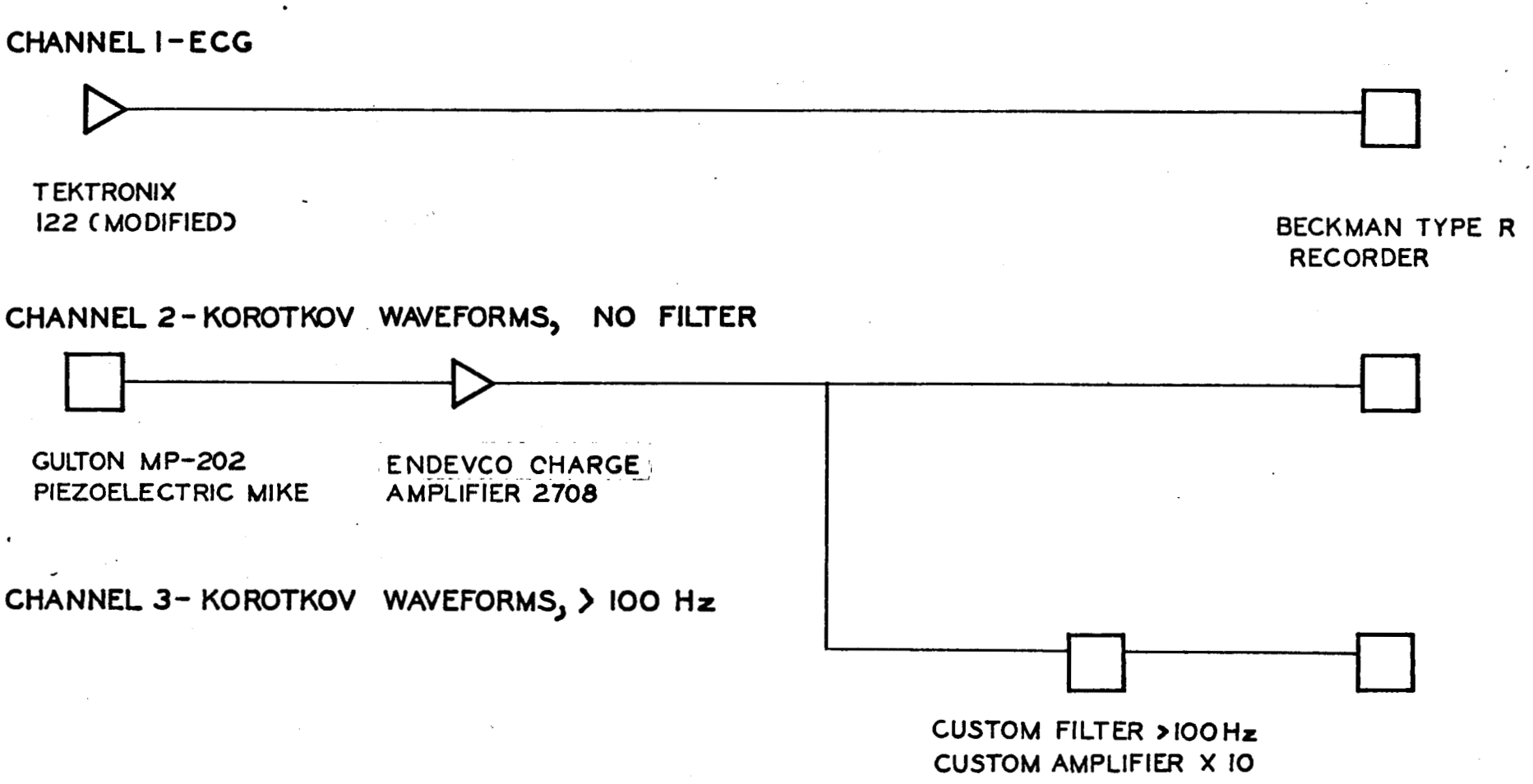


FIG A-I-4 INSTRUMENTATION FOR SAMPLE RECORDINGS

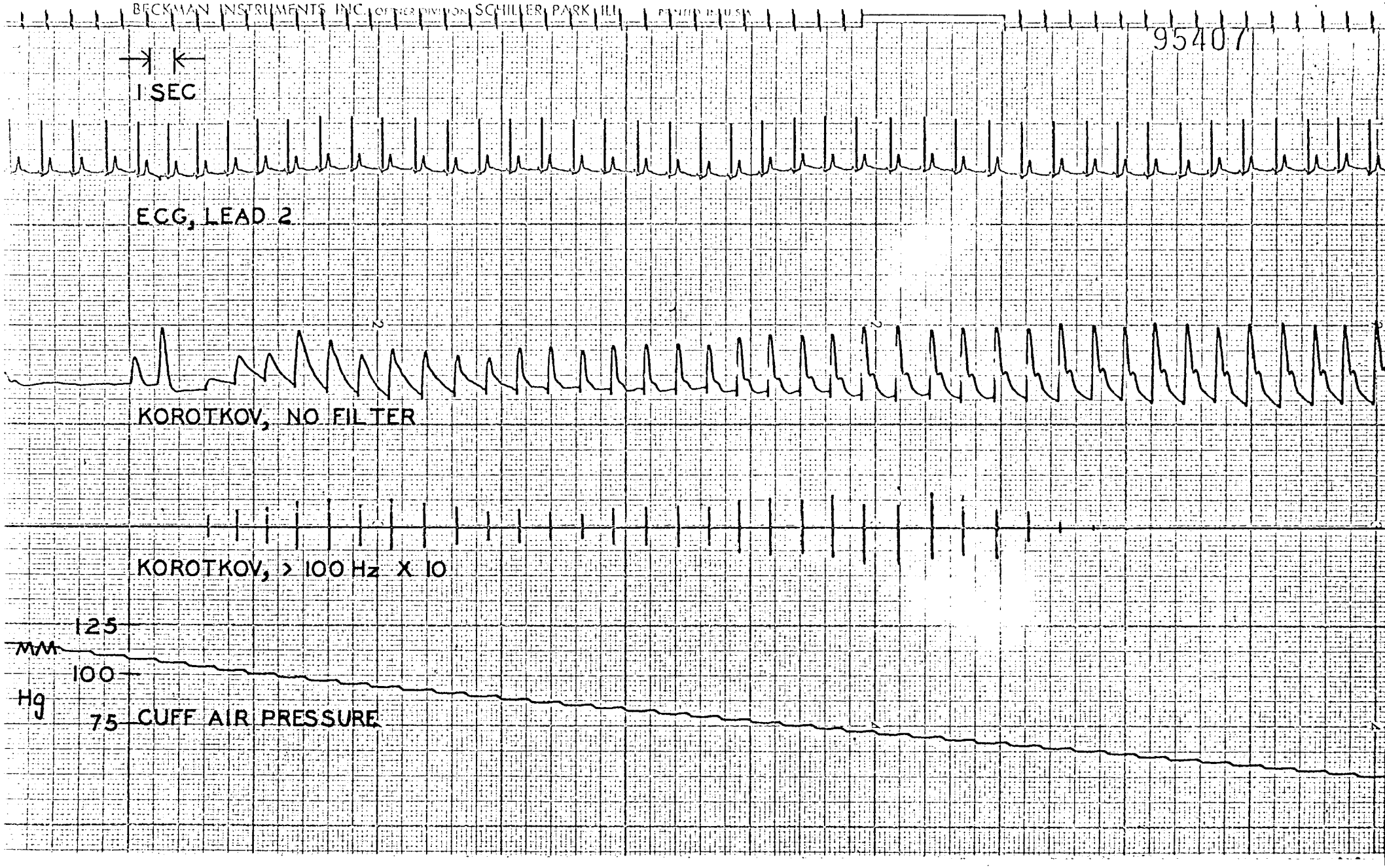


FIG A-I-5 PERFORMANCE OF AUTOMATIC CUFF DEFLATOR

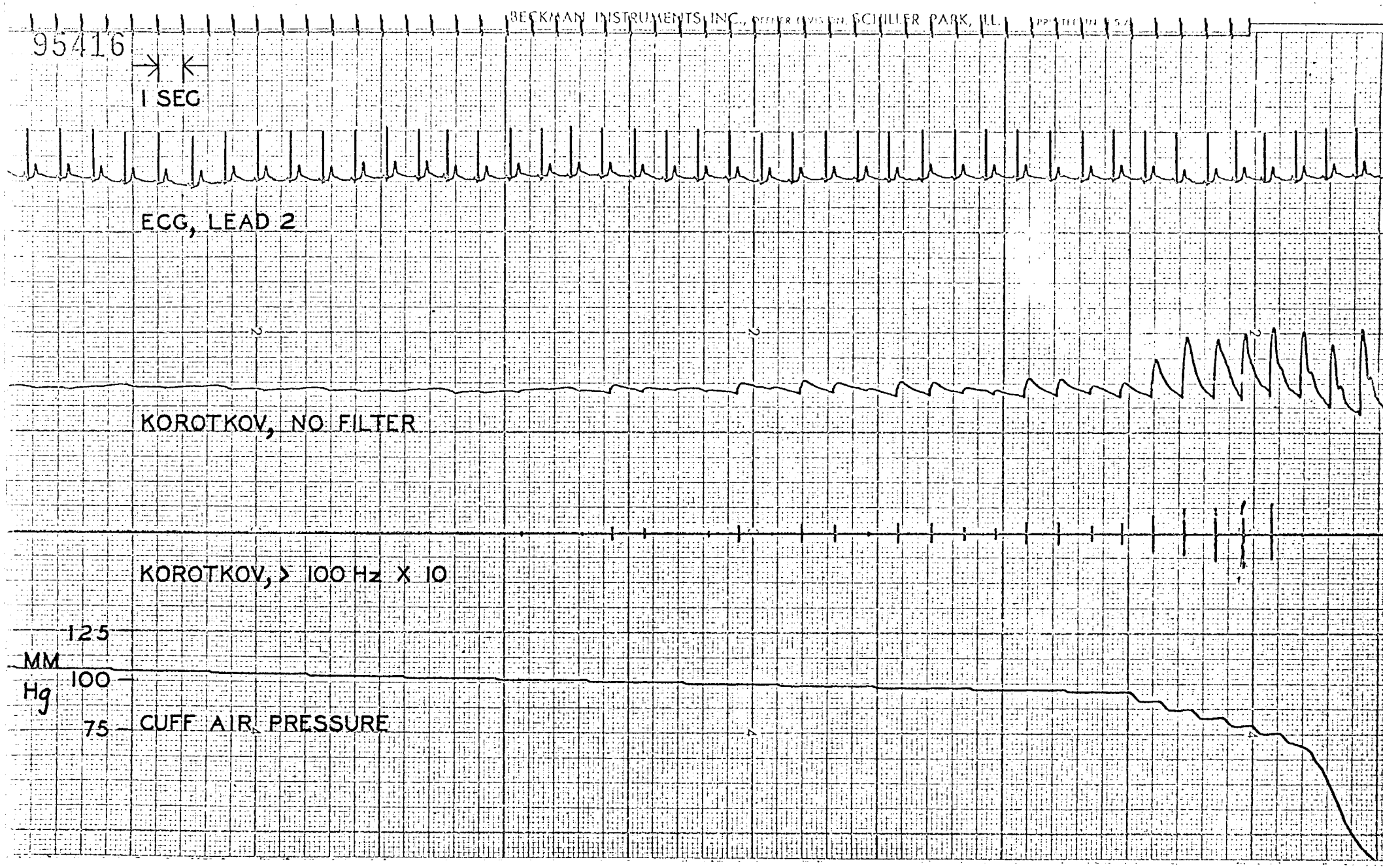


FIG A-I-6 STUDY OF EARLY KOROTKOV WAVEFORMS

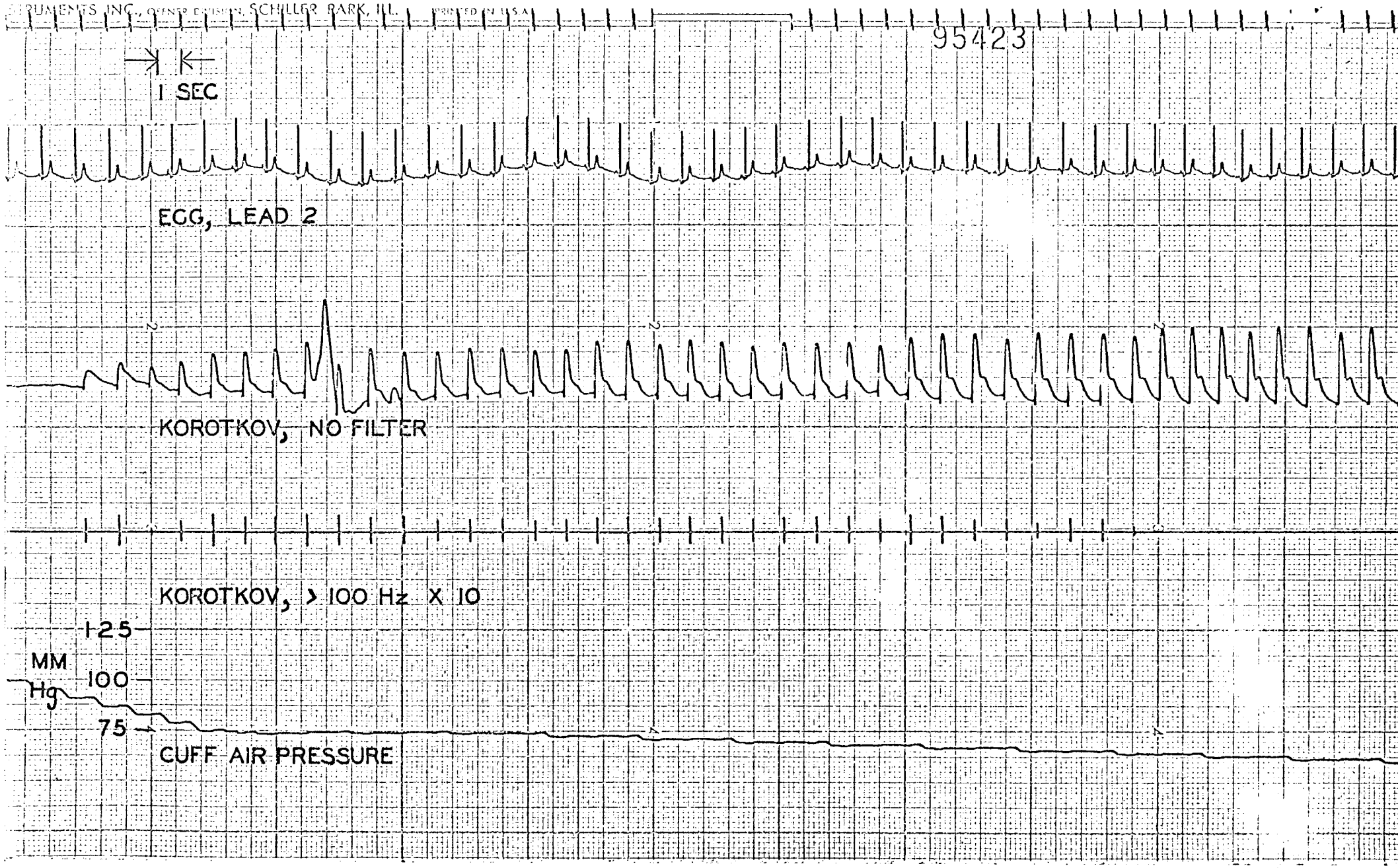


FIG A-I-7 STUDY OF LATE KOROTKOV WAVEFORMS

APPENDIX II. NASA Status Report, July 1967

AUTOMATIC INCREMENTAL BLOOD PRESSURE CUFF DEFLATOR

The long-used manual cuff deflation system appears to have serious shortcommings when detailed Korotkov sound studies are required. First, although the user attempts to follow a linear deflation curve, he is not likely to be successful. Second, because the deflation curve is not linear and because the user cannot maintain synchronization between his subject's heart rate and the deflation curve, Korotkov sounds either may be missed or, in a series of deflations, are unlikely to be seen more than once at a particular pressure level. Third, the cuff pressure is continually dropping (instead of being held at various fixed levels). As a result, the pressure change which occurs between the beginning and end of a Korotkov sound is certain to confound any in-depth spectral analysis of Korotkov sounds. Automatic cuff deflators which essentially parallel the manual deflation systems have the same shortcomings for Korotkov sound analysis.

The automatic incremental blood pressure cuff-deflation system described on the following pages has been specifically designed for Korotkov sound analysis with the above limitations in mind. It is particularly applicable for obtaining frequent blood pressure recordings from the same patient in the operating room, intensive care unit, or possibly (after repackaging) in space flight. The system appears likely to become a key component in the fully automatic recording of indirect arterial blood pressure for research and clinical purposes.

Our design objective - which has been met - is a system that will decrease cuff pressure in discrete steps of height (pressure change) and width (time duration). Pressure changes are made only between the periodic appearance of Korotkov sounds, and are initiated either manually or by pulses developed from the subject's ECG. The system permits Korotkov sound measurements at predetermined (and repeatable) pressure levels. Furthermore, these measurements are made during time intervals when pressure is being held constant by the system. The result should be more meaningful measurements of Korotkov sounds and their spectral distribution.

The deflation system controls the air pressure in the standard clinical blood pressure cuff. Salient features include: (1) reduction of pressure in the cuff in steps of a fixed increment, adjustable from 1 to 5 mm Hg; (2) triggering of each stepwise pressure drop either automatically (generally using each R-wave - or periodically selected R-waves - of the electrocardiogram as a trigger) or manually; (3) adjustable delay between R-wave trigger and cuff pressure drop, ensuring that each Korotkov sound will fall near the center of the horizontal portion of each step, rather than near or on the vertical portion; and (4) adjustable pulse divider system, permitting one or more (up to four) Korotkov sounds to occur on the horizontal portion of each step. Internal calibration and performance checks are provided. A "DUMP" command quickly empties the cuff upon completion of measurements.

The system was initially constructed in "breadboard" style, and this unit is in use. A second unit is being built (Figures A-II-1 through A-II-4) for permanent service. Circuit and physical descriptions and block diagrams follow. Complete schematic drawings will be provided in a subsequent report.

Description of system

The block diagram shown in Figure A-II-5 illustrates the pneumatic and electronic portions of the incremental cuff deflator. The diagram for the triggering sub-system which provides the initiating pulses is shown in Figure A-II-6. The cuff (1A, Figure A-II-5) and reservoir (2A) are initially pressurized to a selected level, say 160- or 200-mm Hg, by a pump (3A) (manual or electric). System pressure is then decreased in steps by opening and closing the solenoid valve (4A) under electronic control. Response of the control system is guided by the output of a pressure transducer (5A) that continually monitors cuff pressure.

A fast-acting solenoid valve (4A) has been provided. The valve requires about 10 msec to open and 10 msec to close. Nevertheless, because the cuff volume is limited, the pressure drop occurring during one cycle (from valve closed to open and return) can be greater than the desired incremental drop. To limit and control the pressure drop, a reservoir (2A) has been placed in parallel with the cuff. Both cuff and reservoir exhaust through the solenoid valve when the valve is energized, and the combined volume of cuff and reservoir is sufficient to prevent undue pressure drop as a result of solenoid response-time limitations.

The main unit (Figure A-II-1) is 19 x 5½ x 10 in. and weighs about 14 lb., including power supplies. Triggering controls and adjustments and a calibration system (subsequently described) are provided. The incremental pressure drop can be set to one of five levels: 1, 2, 3, 4, or 5 mm Hg/ increment. A front panel indicator lamp lights when the solenoid valve is open. The reservoir (not illustrated) is a piece of vinyl tubing ¼ in. in diameter and 120 in. long, and a 1000 ml semi-rigid plastic bottle.

The electronic control system is designed to open the solenoid valve upon receipt of a trigger and to close the valve when system pressure (cuff, reservoir, and interconnecting tubing) has dropped by the desired pressure increment. Operation of the control system is as follows.

Cuff pressure is measured by a transducer (5A) attached to the cuff. The transducer develops a voltage proportional to the cuff pressure, and transducer output varies linearly over a 4-volt range for a 200 mm Hg pressure change. Its output is -2v for 0 mm Hg and +2v for 200 mm Hg. This means that a 2 mm Hg drop leads to an output variation of 40 mv. An amplifier (6A) immediately following the transducer increases the voltage variation for a 200 mm Hg range from ±2v to ±5v, or a voltage change of

100 mv for a 2 mm Hg pressure change. The objective of subsequent circuitry is to process a difference voltage whose current value is based on the transducer output for the previous fixed pressure level of the cuff and the changing output voltage provided by the transducer as cuff pressure drops. This changing (or difference) voltage is amplified 10 X and continually compared against a reference voltage whose value is set at the voltage equivalent to a desired pressure-drop increment (e.g., 10X 100 mv or 1-volt for a 2 mm Hg drop). When the difference voltage agrees with the reference voltage, the solenoid valve is closed and system pressure then remains at a constant level until another command for an incremental pressure drop is received.

Here, in more detail, is the sequence of operation. The output of the transducer amplifier (6A) enters a sample-and-hold circuit (7A) and (8A) which samples the amplified transducer output voltage upon receipt of a 5-msec command trigger from a one-shot multivibrator (9A). This trigger has been derived previously from the heart or manually by the user. As sampling occurs, a pulse sets the flip-flop (10A) and, through the valve driver (11A), opens the valve (4A), which in turn releases air from the cuff (1A) and its parallel reservoir (2A).

The sample-and-hold circuit is composed of a p-channel switch (7A) and a high-impedance unity gain (8A). The difference between the sampled voltage and the voltage appearing ahead of the switch is proportional to the drop in pressure. This voltage difference is amplified 10X by the difference amplifier (12A). When the voltage output reaches the level of the reference source (13A), the comparator (14A) develops an output which triggers the one-shot multivibrator (15A) which in turn resets the flip-flop (10A) and, through the valve driver (11A) response, deenergizes (closes) the solenoid valve. The system now stabilizes at a pressure that is one increment below its previous level, and is ready to receive another trigger pulse to repeat the above cycle.

Provisions are provided for manual or automatic initiation of each cuff deflation cycle (where a cycle is the deflation of the cuff by one increment of pressure). The R-wave from the ECG is the normal initiating source in the automatic operating mode. An adjustable delay between receipt of the R-wave and actual triggering of the deflation cycle permits better positioning of the Korotkov sounds on the horizontal portion of the pressure steps. A frequency divider periodically eliminates a selected number of R-waves so that the cuff pressure may be kept at a fixed pressure for several heart (and Korotkov) cycles.

The triggering subsystem is outlined in Figure A-II-6. The d-c component of the incoming ECG signal may be retained or eliminated by a switch and capacitor (1B). The amplifier (2B) has a gain of 1, 2, 5, 10 or 25X. An inverter (not shown) permits either a positive or negative input from the ECG. Adjustment of the d-c level over a range of -1.8 to +5.0 v, and

without deterioration of the a-c signal, is available (3B). A Schmitt trigger (4B) responds when its input voltage reaches about +5 v. The Schmitt trigger output is delayed by a delay circuit (5B). This delay (provided by a one-shot multivibrator) is adjustable over a period of 80 msec to 1 sec. A transistor in the delay circuit responds only to the trailing edge of the one-shot's output pulse. A shaping stage (not shown) drives the two division flip-flops. The frequency divider (6B) reduces by a desired factor the number of pulses sent on to cycle the cuff deflator via a one-shot multivibrator (8B). The end result is that the user can have each R-wave pulse - or every second, third, or fourth R-wave pulse, as he desires - trigger the cuff deflator. In addition, the user can manually (by pushbutton) cycle the deflator. These selections are made by switch positioning (7B).

Basic system performance and calibration is checked by comparing the internal incremental reference source against a fixed internal reference source representing a cuff pressure increment of 2 mm Hg. Switch positions (Figure A-II-1) are as follows:

Switch			Position
DUMP	OPERATE	CALIBRATE	CALIBRATE
mm Hg	DROP/STEP		2
ADJ.	2 mm Hg/STEP		centered

Manual triggering causes the fixed reference source to be sampled, opens the solenoid valve, and lights the VALVE OPEN indicator. If rotation of the ADJ. 2 mm Hg/STEP control within the indicated limits of -10 and +10 on the panel fails to trip the comparator to close the valve, trouble within the system is indicated. (Check 15-volt ± 5% power supplies as the first step in troubleshooting.) Undesirable d-c drift of the sample-and-hold circuitry can be recognized by (1) increasing the setting of the ADJ. 2 mm Hg/STEP control to its maximum (or to its minimum if the comparator check resulted in a control setting to the left of center); and (2) sampling the internal reference source by pressing the MANUAL button and then measuring the time required for the VALVE OPEN indicator light to go dark. Drift of the sample-and-hold circuitry is excessive if the light goes out in less than 10 sec.

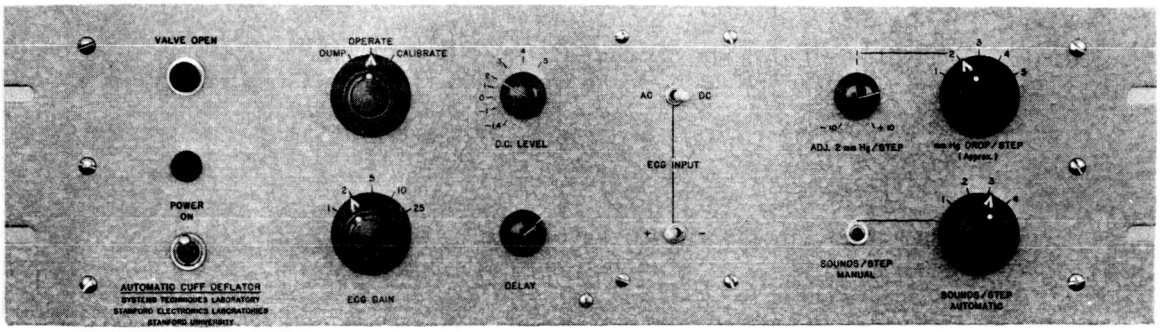


Fig. A-II-1. Front panel of automatic cuff deflator unit. This is the permanent unit that will replace the original "breadboard" unit.

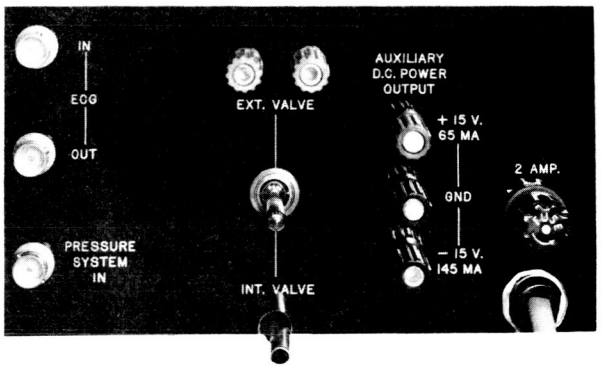


Fig. A-II-2. Back panel of new unit.

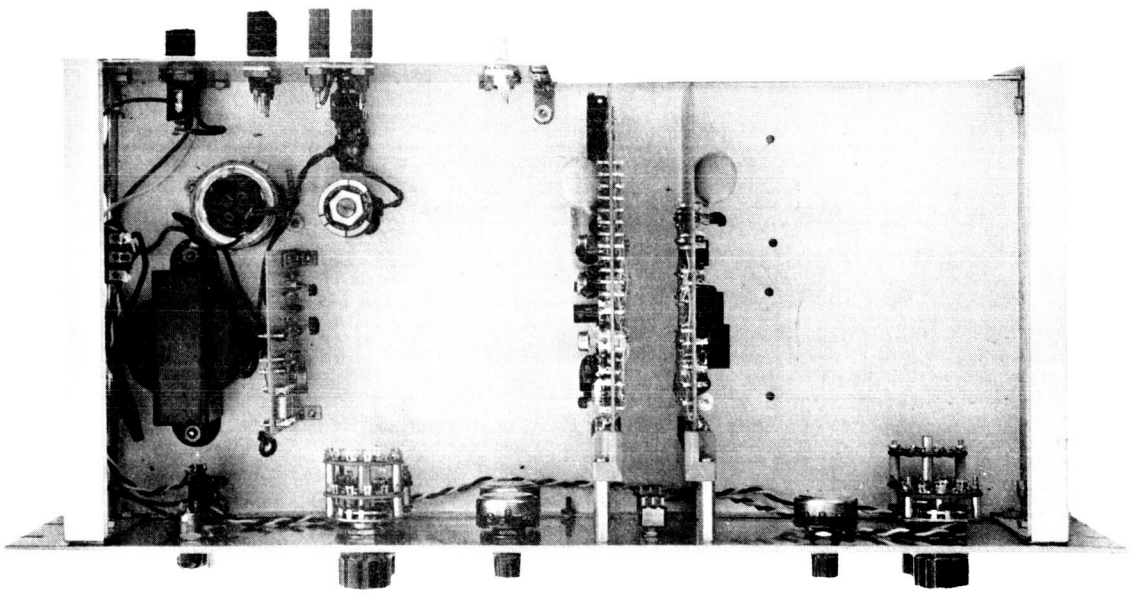


Fig. A-II-3. Top view of new unit. Power supplies had not been installed and construction was incomplete when this photograph was taken.

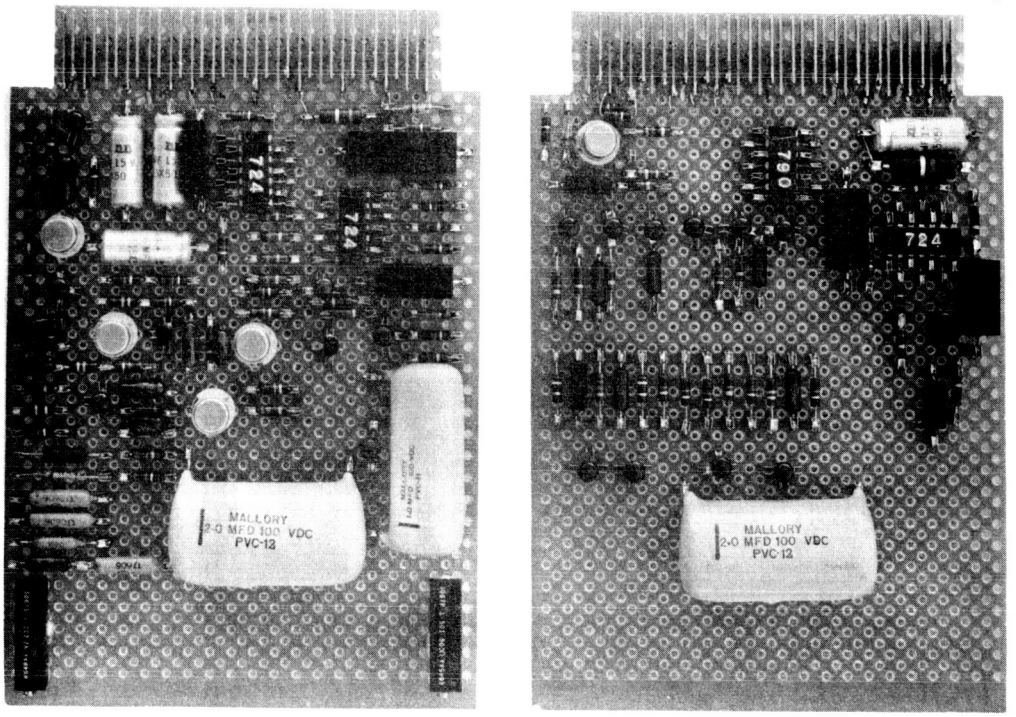


Fig. A-II-4. Top view of circuit board used in permanent unit.

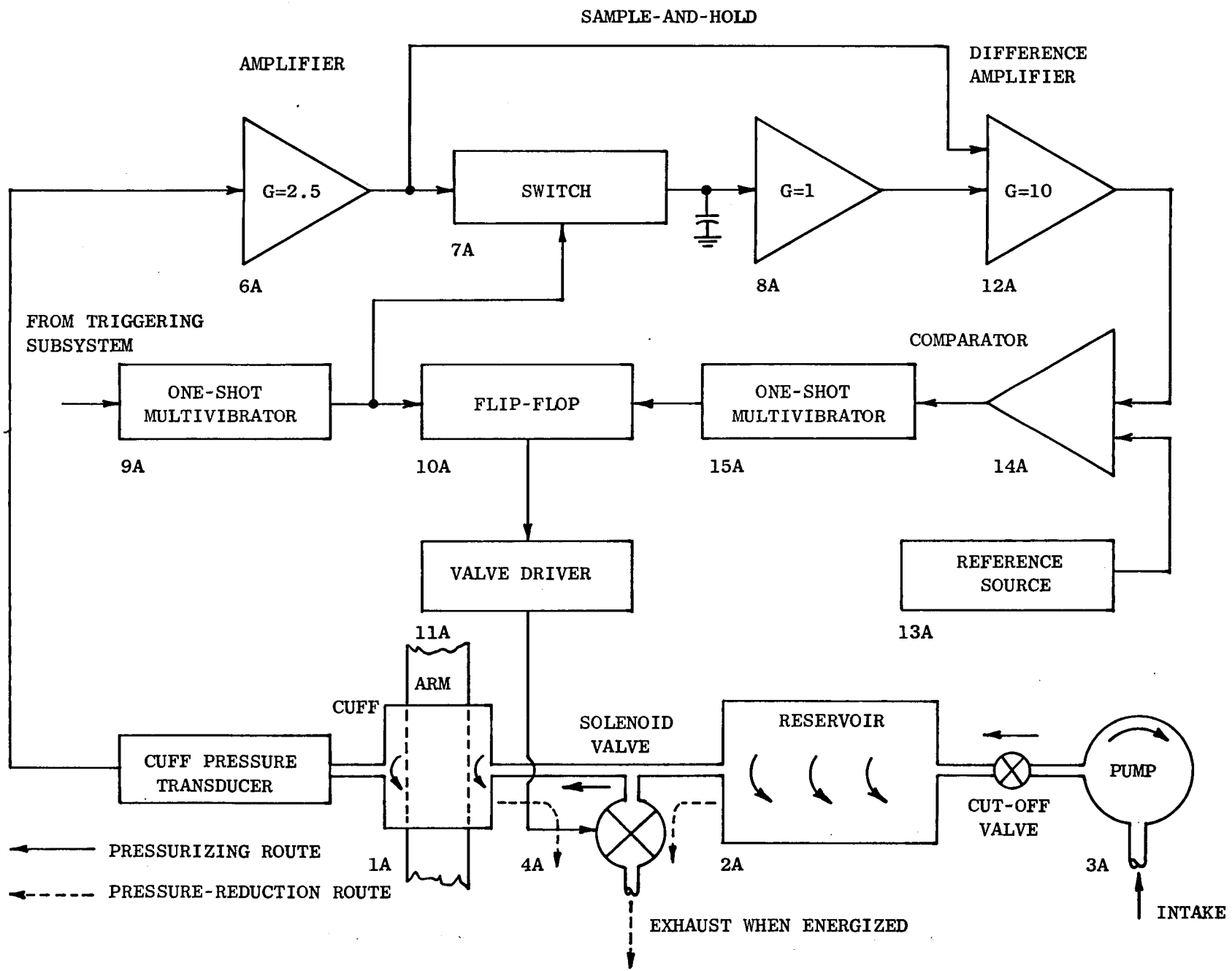


FIG. A-II-5. ELECTRONIC AND PNEUMATIC SYSTEM FOR AUTOMATIC CUFF DEFLATOR.

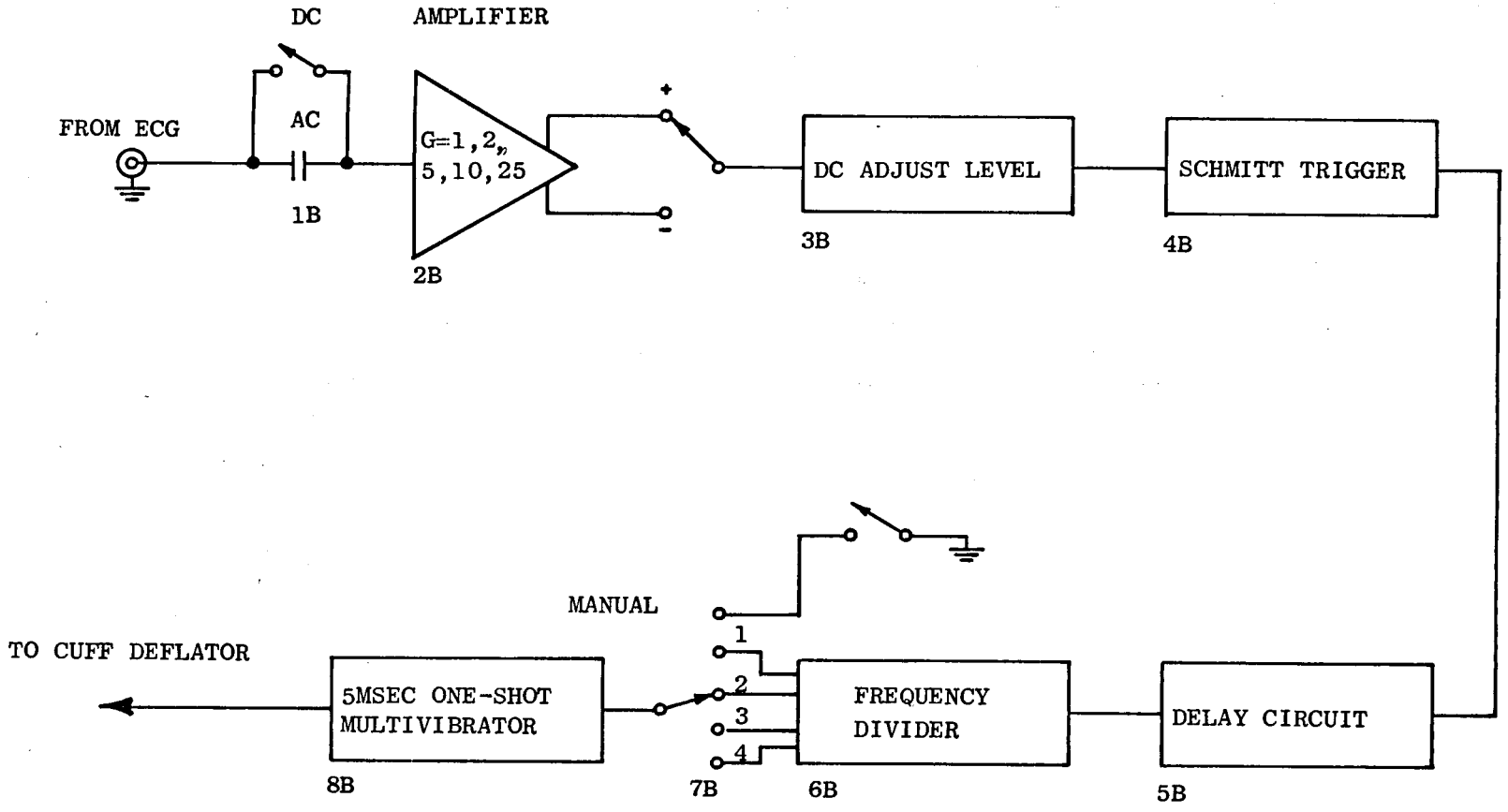


FIG. A-II-6. TRIGGERING SUBSYSTEM FOR AUTOMATIC CUFF DEFLATOR.